UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,395	06/07/2000	Avi J. Ashkenazi	P1759R1	9150

7590 04/25/2002

Genentech Inc
Attn Diane L Marschang
1 DNA Way
South San Francisco, CA 94080

EXAMINER
NICKOL, GARY B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/25/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,395	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-10 and 19-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-10 and 19-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

The Amendment filed February 15, 2002 (Paper No. 9) in response to the Office Action of November 6, 2001 is acknowledged and has been entered.

Claims 6-13, and 19-43 are currently pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Information Disclosure Statement

The replacement IDS filed February 27, 2002 has been considered.

Rejections Withdrawn:

The rejection of claims 6-10, 19, 25-26, and 28 under obviousness-type double patenting (Paper No. 7, page 4) as being unpatentable over claims 1-11, and 13-14 of US Patent No. 6,252, 050 is withdrawn in view of applicant's arguments in Paper No. 9, pages 8-9.

The rejection of Claims 6-13, 19-43 under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,252,050, June 12, 1998 in view of Rougier *et al.* (Semin.Oncol, 1996, Vol. 23, Abstract only) and the rejection of Claims 6-13, 19-43 under 35 U.S.C. 103(a) as being unpatentable over WO 98/51793, November 1998, IDS # 14, in view of Rougier *et al.* (Semin.Oncol, 1996, Vol. 23, Abstract only) are withdrawn. (Paper No. 7, pages 5-8)

Applicants argue (Paper No. 8, page 9) that although certain DR5 antibodies or CPT-11 may be been described in the literature, there was no reasonable expectation that such agents could be combined in a certain manner to achieve a synergistic effect in inducing apoptosis in mammalian cancer cells. This argument has been considered and is found persuasive. However, a recent review of the relevant literature suggests that such synergy between a chemotherapeutic and an apoptosis inducing agent would be achieved:

New Rejections:

Claims 6-13, and 19-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ashkenazi *et al.* (US 6,252,050, June 12, 1998) or Ashkenazi *et al.* (WO 98/51793, November 1998, IDS # 14) in view of Keane *et al.* (Cancer Research, Vol. 59, pages 734-741, February 1999) and Rougier *et al.* (Semin.Oncol, 1996, Vol. 23, Abstract only).

Ashkenzai *et al.* (US 6,252,050 and WO 98/51793) teach as set forth previously in Paper No. 7, pages 5-7.

Rougier *et al.* teach that CPT-11 is a promising anticancer agent which has demonstrated clinical utility in advanced colorectal cancer in more than 400 patients recruited in phase II

clinical trials. Rougier *et al.* further teach that CPT-11 appears to have activity *similar* to that of 5-fluorouracil (5-FU) in first-line treatment.

Keane *et al.* teach that activation of death receptors in the TNF-receptor superfamily provides a specific mechanism to induce apoptosis in breast cancer cells and that DR4 and DR5 are members of the TNF receptor family which are activated by binding the ligand TRAIL, also called Apo-2L (page 734, second column, 1st paragraph). Keane *et al.* further teach that that incubation of cells lines with the chemotherapeutic drugs doxorubicin or 5-fluoruracil significantly augmented TRAIL-induced apoptosis. More specifically, Keane *et al.* teach that "the data demonstrate that the toxicity of the combination of TRAIL and doxorubicin is significantly greater than the toxicity of each agent alone". The authors further report that a similar augmentation of toxicity is demonstrated for TRAIL combined with the chemotherapeutic, 5-fluoruracil (page 737, 2nd column, line 10).

Therefore, it would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to optimize the methods taught by Askenazi *et al.* (US Patent 6,252,050 or WO 98/51793) by including an additional chemotherapeutic agent, CPT-11, since it was well known in the art at the time the invention was made that a) agonistic ligand-activation of death receptors DR4 and DR5 induced apoptosis; b) CPT-11 has shown clinical efficacy in the treatment of advanced colorectal cancer. One would have been motivated to combine the agonistic anti-DR5 receptor antibody of Askenazi *et al.* with CPT-11 because Keane *et al.* have demonstrated that that the toxicity of the combination of TRAIL with either doxorubicin or 5-flurouracil is significantly greater than the toxicity of each agent alone. Moreover, since CPT-11 has been reported to have similar activity as 5-flourouracil, one of ordinary skill in the art would

have a reasonable expectation that the combination of an agonistic anti-DR5 receptor antibody and CPT-11 would augment apoptosis in cancer cells in a synergistic fashion. Lastly, the instant situation parallels the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, given the teaching of the prior art of the clinical efficacy of CPT-11, it would have been obvious to induce apoptosis in mammalian cancer cells including colorectal cancer cells with a synergistically effective amount of agonistic anti-DR5 receptor antibody and CPT-11 because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as anti-cancer agents.

All other rejections and or objections are withdrawn.

The following prior art is provided and made of record (although not relied upon) is considered pertinent to applicant's disclosure: Alnemri *et al.* (PGPUB, US2001/0029030A1, August 14,1998) teach agonistic anti-DR5 antibodies to modulate the activity of the DR5 polypeptide (page 9, 2nd column; page 11, 1st column, last paragraph).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
April 24, 2002